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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,842	03/20/2006	Ania Muntau-Heger	30610/30032	5018

90849 7590 05/13/2010

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EXAMINER	
VAKILI, ZOHREH	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
05/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/539,842	MUNTAU-HEGER ET AL.	
	Examiner	Art Unit	
	ZOHREH VAKILI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1020/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 45-55 are presented for examination.

Applicant's Amendment filed October 20, 2009 has been received and entered into the present application. Claims 41-55 are pending and are herein examined on the merits.

Applicant's arguments, filed October 20, 2009 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

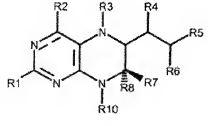
Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

(Maintained)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compound



wherein R1 is selected from the group consisting of: H, OH, SH, F, C1, Br, I, NH2, N(CH3)2, N(C2Hs)2, N(C3H7)2; NH-acyl, wherein the acyl residue contains 1 to 32 carbon atoms; wherein R2 is selected from the group consisting of H, OH, SH, NH2, F, C1, Br, I, O, S; wherein R3 is selected from the group consisting of: H, CH3, C2H5; wherein R4 and R6 are selected independently of each other from the group consisting of: H, OH, SH, NH2, F, C1, Br, I, acetyl, OX, wherein X is a C1 to C32 acyl residue; wherein R5 is selected from the group consisting of: phenyl, CH3, C2H5, C3H7, butyl, isobutyl, t-butyl; wherein R7 and R8 are selected independently of each other from the group consisting of: H, OH, SH, NH2, F, C1, Br, I, CH3, COOH, CHO, COOR9, wherein R9 CH3, C2H5, C3H7, butyl; wherein R10 is selected from the group consisting of: H, CH3, C2Hs, and -- represents an optional double bond, does not reasonably provide enablement for making the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connect, to make the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The presently claimed invention is directed to a method for treating of conditions of reduced protein tolerance due to reduced phenylalanine oxidation without deficiency of cofactor tetrahydrobiopterine.

The instant claims require the administration of a compound of the general formula, wherein R1 is selected from the group consisting of: H, OH, SH, F, C1, Br, I, NH2, N(CH3)2, N(C2Hs)2, N(C3H7)2; NH-acyl, wherein the acyl residue contains 1 to 32 carbon atoms; wherein R2 is selected from the group consisting of H, OH, SH, NH2, F, C1, Br, I, O, S; wherein R3 is selected from the group consisting of: H, CH3, C2H5; wherein R4 and R6 are selected independently of each other from the group consisting of: H, OH, SH, NH2, F, C1, Br, I, acetyl, OX, wherein X is a C1 to C32 acyl residue; wherein R5 is selected from the group consisting of: phenyl, CH3, C2H5, C3H7, butyl, isobutyl, t-butyl; wherein R7 and R8 are selected independently of each other from the group consisting of: H, OH, SH, NH2, F, C1, Br, I, CH3, COOH, CHO, COOR9, wherein R9 CH3, C2H5, C3H7, butyl; wherein R10 is selected from the group consisting of: H, CH3, C2Hs, and -- represents an optional double bond, in order to achieve the claimed therapeutic objective of treating of conditions of reduced protein tolerance. However, the instant specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan of the specific conditions and/or starting materials and/or reaction schema to be used to synthesize the claimed compounds of

the general formula. In the absence of such direction or guidance, the instant specification fails to provide adequate enabling disclosure to practice the full scope of the claimed subject matter.

The disclosure has been fully and carefully considered, it is noted that this same disclosure lacks a clear teaching, direction or guidance as to how to prepare compounds of the instantly claimed general formula. There are none specific teaching to the synthesis of the particular compound under examination and none specific schema in the instant disclosure to provide a method of synthesizing a compound of the structure presently under examination. Moreover, even if this information were actually contained within organic chemistry texts, this information regarding the manner and process of synthesizing the claimed compound is essential subject matter for the practice of the instant invention and cannot be properly incorporated into the instant specification be reference to, e.g., a publication, for such essential subject matter.

Applicant is reminded that the incorporation of essential material in the specification by reference to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. Please see 37 C.F.R. 1.57(f).

Furthermore, it is noted that the execution of chemical reactions is dependent

upon numerous variable factors that are essential for producing the intended compound, such as, but not limited to, the starting materials to be employed, the temperature at which the reaction(s) should be carried out, solvents, reaction catalysts, molar quantities, surface area, pressure, activation energies, etc. In view of such a number of factors, and further in view of the high degree of variability for each single factor that must be taken into account in order to provide an accurate means for producing the claimed compounds of the general formula, the state of the art with regard to chemical reactions in general is highly complex and sufficiently unpredictable such that the skilled artisan would have been required to undertake undue experimentation to determine the exact conditions and manner and/or process of execution to arrive at those conditions that would have been amenable to actually producing the compound of the general formula wherein R1 is selected from the group consisting of: H, OH, SH, F, C1, Br, I, NH2, N(CH3)2, N(C2Hs)2, N(C3H7)2; NH-acyl, wherein the acyl residue contains 1 to 32 carbon atoms; wherein R2 is selected from the group consisting of H, OH, SH, NH2, F, C1, Br, I, O, S; wherein R3 is selected from the group consisting of: H, CH3, C2H5; wherein R4 and R6 are selected independently of each other from the group consisting of: H, OH, SH, NH2, F, C1, Br, I, acetyl, OX, wherein X is a C1 to C32 acyl residue; wherein R5 is selected from the group consisting of: phenyl, CH3, C2H5, C3H7, butyl, isobutyl, t-butyl; wherein R7 and R8 are selected independently of each other from the group consisting of: H, OH, SH, NH2, F, C1, Br, I, CH3, COOH, CHO, COOR9, wherein R9 CH3, C2H5, C3H7, butyl; wherein R10 is selected from the group consisting of: H, CH3, C2Hs, and -- represents an optional

double bond as claimed in the absence of detailed guidance to this effect.

Absent such evidence or reasoning, and further absent any direction or guidance as to how the skilled artisan would go about synthesizing the claimed compound of the general formula, one of ordinary skill in the art would have no alternative recourse but to undertake an exhaustive, and, thus, unduly burdensome, search for ways to synthesize this embodiment of the claimed invention suitable for use in practicing the claimed methods, particularly since the skilled artisan is faced with such a breadth and variety of possible starting materials and reaction schema from which to choose. In addition, it is not readily apparent that the prior art recognized methods of synthesizing the presently claimed compound at the time of the invention (or at least Applicant has failed to point to such information in a document that can be properly incorporated by reference) such that one of ordinary skill in the art would have been able to drawn upon the knowledge already present in the prior art to execute the synthesis of the presently claimed compound of the general formula, absent factual evidence to the contrary.

Applicant has (1) failed to provide any clear general synthetic procedures to the instantly claimed compound of the general formula or (2) failed to provide any working or prophetic examples directed to a possible method and/or manner of synthesis for the instantly claimed compound of the general formula. While the lack of a working embodiment cannot be the *sole* factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the art and the limited direction that Applicant has presented, provides additional weight to the present conclusion of

insufficient enablement in consideration of the *Wands* factors as a whole.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice this aspect of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor or scientist with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to make the full scope of the invention as instantly claimed, given the disclosure and supporting examples provided in the present specification and the state of the art at the time of the invention. In order to actually achieve the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

Claim Rejection(s)—35 USC 103 (Maintained)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

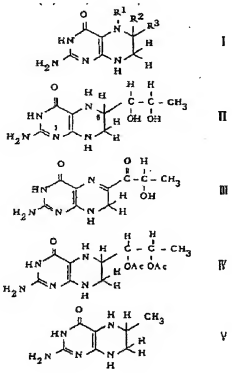
Claims 45-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nichol et al. (US Patent No. 4587340) in view of JP 05194229 (cited on IDS).

Nichol et al. teach a series of pteridines known as pterins which are analogs of tetrahydrobiopterin, to pharmaceutical formulations containing them, to processes for their preparation and to the use thereof in human medicine. More specifically the invention relates to certain biopterin analogs and their use in the treatment of Parkinsonism (and other diseases caused by a deficiency of biogenicamines (e.g.,

catecholamines and serotonin) in the brain and the perpheral nervous system) and the tetrahydrobiopterin-deficient phenylketonurias (atypical PKU) (see col. 1, lines 7-17). Most important neurotransmitters are known to be catecholamines such as dopamine and norepinephrine (noradrenaline) and the indole amine, serotonin (see col. 1, lines 58-61). Tetrahydrobiopterin (BH4) is an essential cofactor for the rate limiting enzymes of biogenic amine synthesis, tyrosine and tryptophan hydroxylases, and for the liver enzyme which converts phenylalanine to tyrosine (see col. 1,lines 62-65). Neurological disorders have been described whose symptoms can be associated with decreases in the number of catecholamine and/or serotonin molecules released at certain synaptic sites. As a category, they may be thought of an `catecholamine-deficiency disorders`. One example is Parkinson's disease (also known as Parkinsonism), where a deficiency in brain dopamine has been linked (see col. 2, lines 3-10). In all of these cases the catecholamines, whose levels are diminished, are formed through the action of tyrosine hydroxylase which is rate-limiting for their formation. This enzyme requires tyrosine, oxygen and a reduced pterin cofactor, tetrahydrobiopterin (BH4), for activity. Levels of this cofactor are severely diminished in Parkinson's disease (see col. 2, lines 21-31). The compound of formula (I) wherein R=C2 H5 is active for tyrosine, tryptophan and **phenylalanine hydroxylases,** whereas the compounds of formula (I) where in R=C3 H7, C4 H9 and C8 H17 are successively less active for tryptophan and **phenylalanine hydroxylases** (see col. 3, lines 5-10) . These compounds will ameliorate the symptoms of endogenous depression by promoting the synthesis of both catecholamines and serotonin in the brain (see col. 3, lines 17-19). In addition to

actions on the central nervous system, the compounds of formula (I) can replace BH4 in the liver and promote the hydroxylation of phenylalanine. A small percentage of all patients with phenylketonuria suffer from a tetrahydrobiopterin-deficient form of phenylketonuria. This "atypical PKU" has been successfully treated with large quantities of BH4. The compounds act as cofactors for hepatic **phenylalanine hydroxylase** to reduce plasma phenylalanine levels. Second, they will act within the brain as cofactors for tyrosine and tryptophan hydroxylase, to correct the BH4 deficient reductions in cerebral catecholamine and serotonin levels which are also seen in atypical PKU. Large amounts of phenylalanine inhibit Phenylalanine hydroxylase with BH4 as cofactor. In contrast, the compounds of formula (I) do not show this substrate inhibition and would remain effective in the presence of large circulating levels of phenylalanine (see col. 3, lines 20-42). Compounds of this invention may be used to treat Parkinson's disease, and other disorders which arise from deficiencies of catecholamines and serotonin at the pre-synaptic sites of neuronal junctions. These compounds may also be used to treat the BH4 -deficient phenylketonurias (atypical PKU) (col. 5, lines 1-7).

JP 05194229 A teaches an agent for treating performance disorders, concentration disorders, paroxysmal anesthesia, akinesia, shivering or emotional unstable type atrabiliary symptom, i.e., nervous diseases, containing a specific pterin derivative as an active ingredient.



A nervous disease-treating agent contains a compound of formula I [R1, R2 are H or together form a single bond; when R1, R2 are the H, R3 is -CH3, L-erythro-CH(OH)CH(OH)CH3," -CH(OCOCH3)CH(OCOCH3)CH3; when R1, R2 are the single bonds, R3 is-COCH(OH)CH3]. The compound of formula I includes L-erythro-5,6,7,8-tetrahydrobiopterin of formula II, L- sepiapterin of formula III, I',2'-diacetyl-5,6,7.8-tetrahydrobiopterin of formula IV and 6-methyl-5,6,7,8-tetrahydropterin of formula. These are effective for the treatment of Parkinson's disease patients and depression patients (see abstract). Formula II reads on the instant claimed invention, see elected compound.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the teachings of the above references and produce a method for the treatment of conditions of reduced protein tolerance due to reduced phenylalanine oxidation comprising the general formula.

In re Kerkhoven (205 USPQ 1069, CCPA 1980) states that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose: the idea of combining them flows logically from their having been individually taught in the prior."

One skilled in the art would have been motivated to employ the teachings of Nichol et al. and JP 05194229, since the above references make clear that the claimed formula has been previously used in a method for treating conditions of reduced protein tolerance. As combined, the references would have resulted in the claimed invention. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, prima facie obvious over the cited arts.

Finally, one would have a reasonable expectation of success given that Nichol et al. and JP 05194229 provide a detailed blueprint for making and using modified compounds of the general formula as claimed, the sequence of which is provided by Nichol et al and JP 05194229, and the steps of which are routine to one of ordinary skill in the art.

Thus the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and as a whole, prima facie obvious.

Response to Argument

Applicant argues it is known in the art how to synthesize tetrahydrobiopterin and other pterin analogs. Also, the specification teaches that compositions useful in the methods have been described in US Patent 4665182.

Applicant's arguments are not persuasive, the specification is not enabled due to improper incorporation by reference. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

Applicant further argues, neither Nichol nor JP05194229 describe what role BH4 would play in correcting a mutation in the PAH gene.

Applicant's arguments are not persuasive, Applicant discusses limitations that are not required by the instant claimed invention. The claims requires the administration of the general formula in the treatment of PKU. Nichols teach pteridines known as pterins which are analogs of tetrahydrobiopterin, to pharmaceutical formulations containing them, and their use in the treatment of Parkinsonism (and other

diseases caused by a deficiency of biogenicamines (e.g., catecholamines and serotonin) in the brain and the perpheral nervous system) and the tetrahydrobiopterin-deficient **phenylketonurias** (atypical PKU) (see col. 1, lines 7-17). This enzyme requires tyrosine, oxygen and a reduced pterin cofactor, tetrahydrobiopterin (BH4), for activity. Levels of this cofactor are severely diminished in Parkinson's disease (see col. 2, lines 21-31). The compound of formula (I) wherein R=C2 H5 is active for tyrosine, tryptophan and **phenylalanine hydroxylases,** whereas the compounds of formula (I) where in R=C3 H7, C4 H9 and C8 H17 are successively less active for tryptophan and **phenylalanine hydroxylases** (see col. 3, lines 5-10) . These compounds will ameliorate the symptoms of endogenous depression by promoting the synthesis of both catecholamines and serotonin in the brain (see col. 3, lines 17-19). In addition to actions on the central nervous system, the compounds of formula (I) can replace BH4 in the liver and promote the hydroxylation of phenylalanine. JP 05194229 teaches the compound of the instant claimed invention. Therefore, both references combined teach every element of the Applicant's invention.

Applicant's arguments were considered in its entirety but failed to be persuasive.

Conclusion

No claims of the present application are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner 1614

May 5, 2010

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614